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Health and Environmental Effects Profile for Chlorthalonil

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CHLORTHALONIL

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16. ABSTRACT

The Health and Environmental Effects Profile for chlorthalonil was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Chlorthalonil has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for chlorthalonil is 2.9×10^{-3} (mg/kg bw/day)$^{-1}$ for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

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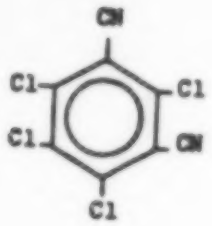
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
ppm	Parts per million
TWA	Time weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Chlorthalonil is known by several synonyms, including 1,3-benzenedicarbonitrile, 2,4,5,6-tetrachloro-3-cyanobenzonitrile, tetrachloroisophthalonitrile and 1,3-dicyanotetrachlorobenzene. A few trade names of this compound are Bravo, Daconil, Exotherm, Exotherm Termil, Forturf, Sweep and Termil (IARC, 1983). The structure of chlorthalonil is given below:



Molecular formula: $C_8Cl_4N_2$

Molecular weight: 265.9

The Chemical Abstracts Service (CAS) Registry number for chlorthalonil is 1897-45-6.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Chlorthalonil in the pure form is a white, odorless, crystalline solid at room temperature. The technical product is ~98% pure and has a slight pungent odor (Worthing and Walker, 1983). Some of the physical properties of chlorthalonil are given below (Worthing and Walker, 1983, unless otherwise stated):

Melting point:	250-251°C
Boiling point:	350°C
Density (temperature unspecified):	1.8 g/cm³ (for the 96% pure compound) (IARC, 1983)
Vapor pressure:	9.75×10^{-9} mm Hg at 40°C

Solubility in water:	0.6 mg/kg at 25°C
Solubility in other solvents:	soluble in acetone, cyclohexanone, dimethylformamide, dimethylsulfoxide, kerosene and xylene
Soil sorption coefficient (based on organic carbon content), K_{oc}:	5800 (estimated) (Kenaga, 1980)
Bioconcentration factor:	820 (estimated) (Kenaga, 1980)
Conversion factor:	1 ppm ~11.05 mg/m³ at 20°C

Chlorthalonil is thermally stable under normal storage conditions (Worthing and Walker, 1983). An aqueous solution of chlorthalonil was found to undergo slow hydrolysis at pH 9. No hydrolysis was observed at pH 7 or lower (Szalkowski and Stallard, 1977). Solutions of chlorthalonil in certain organic solvents were found to be susceptible to photodegradation. This subject is discussed in detail in Chapter 2.

1.3. PRODUCTION DATA

Chlorthalonil can be produced by the chlorination of isophthalonitrile (BCPC, 1977) or by the treatment of tetrachloroisophthaloylamide with phosphorous oxychloride (IARC, 1983).

Diamond Shamrock Corporation, Greens Bayou, TX, is the only U.S. company that presently produces this chemical (SRI, 1983). No production data are available, but it is estimated that the production capacity of chlorthalonil by Diamond Shamrock Corp. is ~5 million kg (IARC, 1983).

1.4. USE DATA

Chlorthalonil is a fungicide used to protect a large number of agricultural crops, especially vegetables, from plant pathogens (Worthing and Walker, 1983). It is also used as a fungicide in nonagricultural products

(Trotz and Pitts, 1981). In 1980, the total estimated U.S. agricultural usage of this compound was 5.0 million kg, with ~53% used on peanuts, 31% on vegetables, 12% on lawns and turf and 5% on potatoes (IARC, 1983). About 0.3 million kg of chlorthalonil was used in the United States in 1978 to control mildew in aqueous emulsion/latex paints (Trotz and Pitts, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Very few comprehensive studies pertaining to the fate and transport of chlorthalonil in any environmental media have been made. The following discussion regarding the fate and transport of this compound in air is speculative and is based on its known or estimated physico-chemical properties.

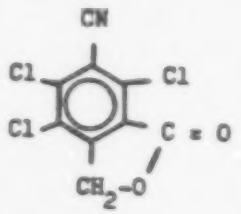
The reactivity of chlorthalonil with the available free radicals and reactive molecules in the atmosphere (i.e., O•, OH•, HO_2, NO_x, O_3, etc.) is not known. As described below, this compound shows photoreactivity with both sunlight and short wavelength UV light when present in certain organic solvents. No study for the photosensitivity of this compound in the gas phase has been made. However, it is unlikely that this compound will be photoreactive with the available sunlight in the atmosphere.

Studies demonstrating the different aspects of atmospheric fate of chlorthalonil are not available. Cupitt (1980), however, presented a mathematical description of a physical removal mechanism to predict the fate of toxic and hazardous materials in the air. For the adsorption of chemicals on aerosol particles, he developed a general model relating the sorption on aerosol surface area with the saturated vapor pressure of a chemical. His results suggest that adsorption will be a reasonable vapor-phase mechanism for removal of air materials with saturation vapor pressure of 10^{-7} mm Hg or less. Since the vapor pressure of chlorthalonil is about 10^{-2} mm Hg at 40°C, this compound may not be significantly sorbed by the aerosol particles in the atmosphere. Both dry and wet deposition may remove some of this compound from the atmosphere.

The fate of chlorthalonil with respect to hydrolysis in aquatic media was studied by Szalkowski and Stallard (1977). No hydrolysis of a 0.5 ppm aqueous solution was observed at pH 7 or less. At pH 9, the compound was

hydrolyzed to 4-hydroxy-2,5,6-trichloroisophthalonitrile and 3-cyano-2,4,5,6-tetrachlorobenzamide. The kinetics for the hydrolysis was observed to be first order and the half-life was found to be 38.1 days at pH 9. Therefore, slow hydrolysis of this compound may take place in ambient alkaline aquatic media.

The photoreactivity of this compound in various organic solvents has been studied by a number of investigators. In some organic solvents, chlorthalonil was found to photoreact readily when exposed to sunligh.. Finley et al. (1979) found that 1 ppm chlorthalonil in benzene disappeared completely in ~30 minutes when the solution was exposed directly to the sun. The product of this reaction was identified as 3,5,6-trichlorobiphenyl-2,4-dicarbonitrile, and the identity was confirmed by several investigators (Khan and Akhtar, 1983; Kawamura et al., 1978; Kohlmann, 1976); however, irradiation with shorter wavelength UV light yielded an additional adduct, 2',5'-dichloro-m-terphenyl-4',6'-dicarbonitrile (Khan and Akhtar, 1983). The photolysis of chlorthalonil is methanol with a medium-pressure mercury lamp produced 2,5,6-trichloro-1,3-dicarbonitrile, 2,5,6-trichloro-4-methyl-1,3-dicarbonitrile and



a lactone of the structure with yields of 2, 9 and 21%, respectively (Binkley et al., 1977). The half-life for the decomposition of chlorthalonil solution in n-hexane (1.0 ppm) when exposed to sunlight was found to be ~45 minutes by Finley et al. (1979). Kohlmann (1976), on the other hand, did not observe any photodegradation of chlorthalonil in n-hexane when

exposed to sunlight. Finley et al. (1979) also found chlorthalonil to be stable in acetone when exposed to sunlight. It is difficult to predict the fate of chlorthalonil in ambient aquatic media exposed to sunlight from these investigations. Since the compound does not undergo photodegradation in all organic solvents, it is likely that is may not undergo significant photodegradation under ambient aquatic conditions.

No comprehensive study pertaining to the aerobic biodegradation of chlorthalonil in aquatic media is available. Nevertheless, Geer (1978) concluded from the value of negative redox potential for this compound that it is unlikely to biodegrade in aquatic media under anaerobic conditions as found in wastewater treatment plants, marshes, flooded soil, stream and lake beds, and ocean floors. Williams (1977) found that chlorthalonil was rapidly metabolized by reticulo-ruminal microorganisms, indicating the possibility of metabolism of this compound by gastrointestinal microflora.

No experimental study determining the bioconcentration of this compound in edible aquatic organisms could be found. Using the known water solubility data and binary regression equation, Kenaga (1980) predicted that the BCF for chlorthalonil would be 820. If one considers the BCF for PCBs and DDT, which are known to bioconcentrate in aquatic organisms, to be in the range of 10^4 to 10^5 (Callahan et al., 1979), a value of 820 for chlorthalonil indicates that chlorthalonil may not bioconcentrate appreciably in aquatic organisms.

Little is known about the fate of chlorthalonil in soils. In one investigation, the half-life of chlorthalonil in soil was found to be 3-5 weeks (Anonymous, 1979). It was also found that the chlorthalonil residue remained primarily in a layer 1 cm below the soil surface.

3. EXPOSURE

No reports indicating the levels of chlorthalonil in ambient air or aquatic media could be found. The U.S. EPA's STORET data base (see Appendix A) contains no data concerning the concentration of this compound in aquatic media. Chlorthalonil residues were measured in 23 crop samples in Japan in 1979 (Soma et al., 1980). Residue levels were relatively high in tomato, cucumber and eggplant as compared to levels in cabbage, watermelon and strawberry. A maximum level of 0.543 ppm was detected in eggplant. Residues in watermelon, cucumber and tomato ranged from not detected to 0.003 ppm, not detected to 0.021 ppm and not detected to 0.318 ppm, respectively. The detection limit was not given in the abstract. In a Canadian total diet survey, chlorthalonil was detected in one of six composite samples of garden fruits at levels >20 µg/kg (IARC, 1983). No residue of chlorthalonil was detected in the total diet studies conducted in the United States during 1976-1977 (limit of detection, <0.01 mg/kg) and in Sweden during 1979 (limit of detection, 0.005 mg/kg) (IARC, 1983).

4. PHARMACOKINETICS

4.1. ABSORPTION

Chin et al. (1981) examined the oral, respiratory and dermal absorption of uniformly [^{14}C]-ring labeled chlorthalonil by male Sprague-Dawley rats. The mean percents of [^{14}C]-chlorthalonil equivalents found in the blood of rats at 2.5, 4, 24 and 48 hours after oral, endotracheal and dermal administration are given in Table 4-1. Relative absorption of chlorthalonil was greatest following endotracheal intubation and least following dermal application; however, the highest recorded level of [^{14}C] in the blood of rats treated endotracheally was only 5.2%, reached at 2.5 hours after dosing. In an earlier study, Chin et al. (1980) also concluded that minimal gastrointestinal absorption by rats of orally administered, uniformly [^{14}C]-ring labeled chlorthalonil occurred. The conclusion was based on the findings that $\geq$85% of the administered radioactivity was excreted in the feces within 4 days following dosing, and that a mean of 2.65% of the administered radioactivity was recovered in the bile of rats with duodenal catheters and external biliary fistulae. Urinary excretion data indicated low levels of absorbed chlorthalonil following oral, endotracheal or dermal administration to rats (Section 4.4.) (Chin et al., 1980, 1981).

4.2. DISTRIBUTION

Following oral, endotracheal or dermal exposure to uniformly [^{14}C]-ring labeled chlorthalonil, small percentages of radioactivity were distributed to the blood of rats (see Section 4.1.) (Chin et al., 1980, 1981). As shown in Table 4-1, the peak levels were 5.2% of the administered radioactivity at 2.5 hours after endotracheal dosing, 0.35% at 2.5 hours after oral dosing and 0.27% at 48 hours after dermal dosing.

TABLE 4-1

Mean Percents of [^{14}C]-Chlorthalonil Equivalents Found in the Blood of Rats Following Endotracheal, Oral and Dermal Administration of [^{14}C]-Chlorthalonil*

Time of Sampling (hours)	Endotracheal	Oral	Dermal
2.5	5.2	0.35	0.03
5	3.9	0.11	0.06
24	4.1	0.15	0.11
48	3.7	0.23	0.27

*Source: Chin et al., 1981

4.3. METABOLISM

Pertinent data regarding the metabolism of chlorthalonil were not located in the available literature.

4.4. EXCRETION

Chin et al. (1980) administered uniformly [^{14}C]-labeled chlorthalonil orally to rats, and found $\geq$85 and 8% in the feces and urine, respectively, within 4 days. Chin et al. (1980) suggested that chlorthalonil and/or its impurities may undergo enterohepatic circulation, since 2.65% of the administered radioactivity was recovered in the bile of rats with duodenal catheters and external biliary fistulae 24 hours after oral dosing at 5 mg/kg.

Following endotracheal, oral and dermal administration of uniformly [^{14}C]-labeled chlorthalonil to rats, Chin et al. (1981) found 5.7, 2.9 and 0.9%, respectively, of [^{14}C]-chlorthalonil equivalents in the urine of treated animals at 24 hours, and 0.7, 0.7 and 0.8%, respectively, at 48 hours.

5. EFFECTS

5.1. CARCINOGENICITY

Groups of 50 male and 50 female B6C3F1 weanling mice and 50 male and 50 female Osborne-Mendel weanling rats were given technical grade (98-98.5% pure) chlorthalonil ad libitum in the diet for 80 weeks (NCI, 1978). The male mice were given TWA doses of 2688 or 5375 ppm, while female mice received TWA doses of 3000 or 6000 ppm. Both sexes of rats were given TWA doses of 5063 or 10,126 ppm. For mice, control animals consisted of two groups: matched controls comprised of 10 animals of each sex and pooled controls comprised of 50 animals of each sex from similar bioassays of five other test chemicals performed at the same laboratory, each of which received 2% corn oil in their feed. For rats, control animals also consisted of two groups: matched controls comprised of 10 animals of each sex and pooled controls comprised of 55 animals of each sex from similar bioassays of five other test chemicals performed at the same laboratory, each of which received 2% corn oil in their feed. Observation periods after exposure were 11-12 weeks for mice and 30-31 weeks for rats. Surviving animals were killed at 91-92 weeks (mice) or 110-111 weeks (rats).

Similar survival rates were reported for all groups of treated mice and treated female rats; survival was significantly decreased ($p=0.002$) for high dose and low dose. This decrease in survival occurred after week 75 of treatment. There was no significant difference in tumor incidence between treated and control mice that the authors considered to be treatment-related. A statistically significant dose-related trend in renal tubular epithelial adenomas and carcinomas was reported for both male ($p=0.03$) and female ($p=0.007$) rats. The incidences of renal tubular epithelial adenomas and carcinomas were 0/62 pooled male controls, 3/46 low-dose males, 4/49

high-dose males, 0/62 pooled female controls, 1/48 low-dose females and 5/50 high-dose females. The incidences were significantly different from control for the high-dose male (p=0.035) and the high-dose female groups (p=0.016). There was no treatment-related significant difference in other tumor incidences for rats. IARC (1983) considered this evidence of carcinogenicity in rats to be limited.

5.2. MUTAGENICITY

Chlorthalonil has been tested for genotoxicity in several systems. These genotoxicity assays are summarized in Table 5-1.

Equivocal results for chlorthalonil have been reported for the reverse mutation assay with Salmonella typhimurium. Both Jeang and Li (1978) and Zhang et al. (1980) reported positive responses for chlorthalonil, but these studies were only available as abstracts; therefore, details regarding the use of an exogenous metabolic activating system, application and concentration of chlorthalonil tested were not reported. Several other investigators reported negative results for chlorthalonil in the reverse mutation assay with S. typhimurium in both the presence and absence of a mammalian metabolic activation system (Moriya et al., 1983; Wei, 1982; Jeang and Li, 1980; Quinto et al., 1981).

Jeang and Li (1978) obtained positive results for chlorthalonil in the reverse mutation assay with Bacillus subtilis. Chlorthalonil was negative in the reverse mutation assay with Escherichia coli, strain WP2 hcr, with and without mammalian metabolic activation (Moriya et al., 1983); in mitotic gene conversion assays with Saccharomyces cerevisiae and Aspergillus nidulans (De Bertoldi et al., 1980); and in the mitotic nondisjunction assay with A. nidulans (Morpurgo et al., 1979).

TABLE 5-1

Genotoxicity Testing of Chlorthalonil

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Reference
Reverse mutation	Salmonella typhimurium, strains NR	NR	NR	NR	+	Jeang and Li, 1978
Reverse mutation	S. typhimurium, strains NR	NR	NR	NR	+	Zhang et al., 1980
Reverse mutation	S. typhimurium	plate incorporation	≤5000 µg/plate	±S-9		Moriya et al., 1983
	TA98				-	
	TA100				-	
	TA1535				-	
	TA1537				-	
	TA1538				-	
Reverse mutation	S. typhimurium	plate incorporation	0.764, 7.64, 76.4 and 764 µg/plate	±S-9		Wei, 1982
	TA98				-	
	TA100				-	
	TA1535				-	
	TA1537				-	
	TA1538				-	
Reverse mutation	S. typhimurium	NR	NR	±S-9		Jeang and Li, 1980
	TA98				-	
	TA100				-	
Reverse mutation	S. typhimurium, 5 strains, NOS	NR	NR	±S-9	-	Quinto et al., 1981
Reverse mutation	Escherichia coli, strain WP2 hcr	plate incorporation	≤5000 µg/plate	±S-9	-	Moriya et al., 1983
Reverse mutation	Bacillus subtilis, strains NR	NR	NR	NR	+	Jeang and Li, 1978
Mitotic gene conversion	Saccharomyces cerevisiae	NR	NR	±S-9	-	De Bertoldi et al., 1980
Mitotic gene conversion	Aspergillus nidulans	NR	NR	none	-	De Bertoldi et al., 1980
Mitotic nondisjunction	A. nidulans	plate test, liquid test	≤3.0 µM	none	-	Morpurgo et al., 1979

NR = Not reported; NOS = Not otherwise specified

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of chlorthalonil were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the reproductive effects of chlorthalonil were not located in the available literature.

5.5. CHRONIC TOXICITY

In a NCI cancer bioassay, groups of 50 male and 50 female B6C3F1 weanling mice and 50 male and 50 female Osborne-Mendel weanling rats were given technical grade (98-98.5% pure) chlorthalonil ad libitum in the diet for 80 weeks (NCI, 1978). Male mice were given TWA doses of 2688 or 5375 ppm, while female mice received TWA doses of 3000 or 6000 ppm. Both sexes of rats were given TWA doses of 5063 or 10,126 ppm. For mice, control animals consisted of two groups: matched controls comprised of 10 animals of each sex and pooled controls comprised of 50 animals of each sex from similar bioassays of five other test chemicals performed at the same laboratory, each of which received 2% corn oil in their feed. For rats, control animals also consisted of two groups: matched controls comprised of 10 animals of each sex and pooled controls comprised of 55 animals of each sex from similar bioassays of five other test chemicals performed at the same laboratory, each of which received 2% corn oil in their feed. Observation periods after exposure were 11-12 weeks for mice and 30-31 weeks for rats. Surviving animals were killed at 91-92 weeks (mice) or 110-111 weeks (rats).

Similar survival rates were reported for treated female rats; survival was significantly decreased ($p=0.002$) for treated male rats. A significant dose-related decrease in mean body weight was reported for both sexes of rats. Treated rats had rough hair coats during the first 52 weeks of the

study, but general appearance and behavior were considered to be normal during this time period. During the second year of the study, however, treated rats at both dose levels were observed to have weight loss, decreased food consumption, rough hair coats, pale mucous membranes, ataxia, tachypnea, epistaxis, dermatitis, hematuria, hyperactivity and vaginal bleeding. A statistically significant increase in the incidence of renal tubular epithelial adenomas and carcinomas was seen in both sexes (see Section 5.1.).

Similar survival rates were reported for all groups of treated mice. A significant dose-related decrease in mean body weight was reported for male mice, but not female mice. General appearance and behavior were considered to be normal during the first 52 weeks of the study, with the exception of a few mice with alopecia and hyperexcitability. In the second year of the study, both dose levels of both sexes had low incidences of alopecia, weight loss, rough hair coats, abdominal distention and nodular masses (majority in the lower abdomen). Intermittent swollen testes were observed in both groups of treated males. Hyperexcitability was seen in most males of both the low- and high-dose groups, starting during week 62. There was no significant difference in tumor incidence between treated and control mice that was considered to be treatment-related (see Section 5.1.).

5.6. OTHER RELEVANT INFORMATION

The oral LD_{50} for chlorthalonil in rats was reported to be >10,000 mg/kg (Spencer, 1973). The oral and intraperitoneal LD_{50}s for chlorthalonil in mice were reported as 6000 and 2.5 mg/kg, respectively (Yoshikawa and Kawai, 1966).

Chlorthalonil reduced the active transport of glucose through the isolated intestine of mice (Guthrie et al., 1974).

Patch tests on patients with pesticide-induced contact dermatitis resulted in highly positive reactions for chlorthalonil (Horiuchi and Ando, 1980; Horiuchi et al., 1980; Yamaguchi et al., 1980).

6. AQUATIC TOXICITY

6.1. ACUTE

The only available information concerning the acute toxicity of chlorthalonil to aquatic organisms was provided by Schneider (1979). A formulation containing 98.0% active ingredient yielded a 96-hour LC_{50} value of 0.051 ppm for bluegills, Lepomis macrochirus. Another formulation (wettable powder, 75% active ingredient) produced 96-hour LC_{50} values of 0.167 ppm for bluegills and 0.103 ppm for rainbow trout, Salmo gairdneri.

6.2. CHRONIC

Pertinent data regarding the chronic effects of chlorthalonil were not located in the available literature.

6.3. PLANT EFFECTS

Pertinent data regarding the effects of chlorthalonil on aquatic plants were not located in the available literature.

6.4. RESIDUE

Pertinent data regarding chlorthalonil residues in aquatic organisms were not located in the available literature.

6.5. OTHER RELEVANT INFORMATION

Other relevant information regarding chlorthalonil in the aquatic environment was not found in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The temporary human ADI for chlorthalonil was set in December, 1981, at 0-0.005 mg/kg bw by the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (FAO, 1982).

Tolerances for residues of chlorthalonil on food commodities have been recommended by the WHO Expert Group on Pesticide Residues (ranging from 0.1-30 ppm on various fruit and vegetables) (WHO, 1975), by the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (ranging from 0.05-25 ppm on various fruits and cereals) (FAO, 1978, 1979, 1980), and by the U.S. EPA (ranging from 0.1-15 ppm on 21 various fruits and vegetables) (U.S. EPA, 1980).

7.2. AQUATIC

Existing guidelines and standards for chlorthalonil in the aquatic environment were not found in the available literature.

8. RISK ASSESSMENT

Equivocal results have been obtained in mutagenicity assays of chlorthalonil. No data regarding the teratogenic or other reproductive effects of chlorthalonil were encountered. Mice given chlorthalonil at dietary concentrations (TWA doses) of 2688 or 5375 ppm (males) or 3000 or 6000 ppm (females) for 80 weeks had alopecia, weight loss, rough hair coats, abdominal distention and nodular masses (NCI, 1978). Male mice also had intermittent swollen testes and were hyperexcitable. Rats given chlorthalonil at dietary concentrations (TWA doses) of 5063 or 10,126 ppm (both sexes) for 80 weeks had weight loss, decreased food consumption, rough hair coats, pale mucous membranes, ataxia, tachypnea, epistaxis, dermatitis, hematuria, hyperactivity and vaginal bleeding (NCI, 1978).

In the NCI (1978) cancer bioassay, the incidence of renal tubular epithelial adenomas and carcinomas for both sexes was significantly increased in the high-dose groups. The incidences of renal tubular epithelial adenomas and carcinomas for males were 0/62 pooled controls, 3/46 low-dose and 4/49 high-dose ($p=0.035$); for females, these incidences were 0/62 pooled control, 1/48 low-dose and 5/50 high-dose ($p=0.016$). There was no significant difference in tumor incidence between treated and control mice that was considered to be treatment-related.

Using the cancer data for rats from the NCI (1978) study, a quantitative risk criterion can be derived for chlorthalonil. Because of the absence of food consumption data, the assumption that a rat consumes a daily amount of food equivalent to 5% of its body weight must be made. Using this assumption, an equivalent dose of 506.3 mg/kg/day can be calculated for the high-dose level. Based on the renal tubular epithelial adenoma and carcinoma response of male rats (4/49 treated vs. 0/62 control rats, $p=0.035$) and of

female rats (5/50 treated vs. 0/62 control rats, p=0.016), and using the linearized multistage model adopted by the U.S. EPA (Federal Register, 1980), carcinogenic potency factors (q_1^*) of 2.86×10^{-3} and 2.59×10^{-3} $(mg/kg/day)^{-1}$, respectively, can be derived for humans. The conversion factor used in the calculation of these q_1^* values for humans (assuming 70 kg body weight) from animal data was the cube root of the body weight ratio (Federal Register, 1980), which has been demonstrated to adjust especially for species to species extrapolation. The greater potency factor of 2.86×10^{-3} $(mg/kg/day)^{-1}$ is chosen to represent human carcinogenic risk as a result of exposure to chlorthalonil. Complete data for derivation of the q_1^*s are presented in Appendices B and C.

It should be noted that the above q_1^* values were based upon a study conducted by Gulf South Research Institute under contract to NCI (1978). The results of some of the bioassays conducted by Gulf South Research Institute have been called into question by the National Toxicology Program (NTP, formerly NCI) (Cooper, 1983). The bioassay on chlorthalonil, however, was not specifically mentioned in the news item. IARC (1983) concluded that the available data provide limited evidence that chlorthalonil is carcinogenic to experimental animals.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal studies, but the risk assessment is not altered by these data.

9. REFERENCES

Anonymous. 1979. Investigation of pesticide residues in soil. Annu. Rep. Hiroshima Pref. Agric. Exp. Stn. 1978: 24. (Taken from PESTAB 80:0328)

Binkley, R.W., G.L. Kirstner, V.C. Opaskar and P. Olynyk. 1977. Photochemical reaction of 2,4,5,6-tetrachloroisophthalonitrile. Chemosphere. 6(4): 163-166.

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-Related Environmental Fate of 129 Priority Pollutants. Vol. I. Office of Water Planning and Standards, Office of Water and Waste Management, U.S. EPA, Washington, DC. EPA 440/4-79-029a.

Chin, B.H., R.D. Heilman, R.T. Bachand, G. Chernenko and J. Barrowman. 1980. Absorption and biliary excretion of chlorthalonil and its metabolites in the rat. Toxicol. Lett. 5(Suppl. 1): 150.

Chin, B.H., J.B. McGloin, N.L. Spangler and R.D. Heilman. 1981. Chlorothalonil equivalents in the blood and urine of rats following oral, endotracheal, and dermal administration of 14C-chlorothalonil. Bull. Environ. Contam. Toxicol. 26(1): 258-261.

Cooper, C., Ed. 1983. Cloud Thrown Over NTP Testing of Solvents, Other Chemicals. In: Pesticide and Toxic Chemical News, August 3, 1983. p. 42-43.

Cupitt, L.T. 1980. Fate of Toxic and Hazardous Materials in the Air Environment. Environmental Sciences Research Laboratory, Office of Research and Development, U.S. EPA, Research Triangle Park, NC. EPA 600/3-80-084.

De Bertoldi, M., M. Griselli, M. Giovannetti and R. Barale. 1980. Mutagenicity of pesticides evaluated by means of gene conversion in Saccharomyces cerevisiae and in Aspergillus nidulans. Environ. Mutagen. 2(3): 359-370. (CA 94:42342)

FAO (Food and Agricultural Organization). 1978. Pesticide Residues in Food: 1977 Evaluations. FAO, Rome. p. 87-99. (Cited in IARC, 1983)

FAO (Food and Agricultural Organization). 1979. Pesticide Residues in Food: 1978 Evaluations. FAO, Rome. p. 79-83. (Cited in IARC, 1983)

FAO (Food and Agricultural Organization). 1980. Pesticide Residues in Food: 1979 Evaluations. FAO, Rome. p. 137-148. (Cited in IARC, 1983)

FAO (Food and Agricultural Organization). 1982. Pesticide Residues in Food: 1981 Evaluations. FAO, Rome. p. 17-18. (Cited in IARC, 1983)

Federal Register. 1980. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Criteria Documents. 45: 79347-79357.

Finley, E.L., J.B. Graves, F.C. Hewitt, et al. 1979. Reduction of methyl parathion residues on clothing by delayed re-entry and laundering. Bull. Environ. Contam. Toxicol. 22: 598-602.

Geer, R.D. 1978. Predicting the anaerobic degradation of organic chemical pollutants in waste water treatment plants from their electrochemical reduction behavior. Office of Water Research and Technology, Washington, DC. 61 p. NTIS PB 289224.

Guthrie, F.E., P.V. Shah and D.E. Moreland. 1974. Effects of pesticides on active transport of glucose through the isolated intestine of the mouse. J. Agric. Food Chem. 22(4): 713-715.

Horiuchi, N. and S. Ando. 1980. Conact dermatitis due to pesticides for agricultural use. Nippon Hifuka Gakkai Zasshi. 90(3): 289. (Jap.) (Taken from PESTAB 80:1644)

Horiuchi, N., S. Ando and Y. Kambe. 1980. Dermatitis due to pesticides for agricultural use. Nippon Hifuka Gakkai Zasshi. 90(3): 277. (Jap.) (Taken from PESTAB 80:1643)

IARC (International Agency for Research on Cancer). 1983. Chlorothalonil. In: Miscellaneous Pesticides. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 30. IARC, Lyon, France. p. 319-328.

Jeang, C-L. and G-C. Li. 1978. Screening of mutagenic pesticides using microbial systems. K'o Hsueh Fa Chan Yueh K'an. 6(8): 780-788. (Ch.) (CA 90:198541b)

Jeang, C-L. and G-C. Li. 1980. Screening of pesticides for mutagenicity in the microbial system: 2. With mammalian microsomal activation. Natl. Sci. Counc. Mon. 5(8): 551-559. (Taken from HEEP 81:3470)

Kawamura, Y., M. Takeda and M. Uchiyama. 1978. Photolysis of chlorothalonil in benzene. Nippon Noyaku Gakkaishi. 3(4): 397-400. [CA 91(5):39097r]

Kenaga, E.E. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol. Environ. Safety. 4: 26-38.

Khan, S.U. and M.H. Akhtar. 1983. Photodecomposition of chlorothalonil in benzene. Pestic. Sci. 14: 354-358.

Kohlmann, H. 1976. Mass spectrometric study of the photoreaction of chlorthalonil. Land-Forstwirtsch. Forsch. Oesterr. 7: 135-138. (Ger.) [CA 86(15):101775n]

Martin, H. and C.R. Worthing, Ed. 1977. Pesticide Manual. BCPC Publications, Worcestershire, England. p. 113.

Moriya, M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116(3-4): 185-216. (CA 98:156179z)

Morpurgo, G., D. Bellincampi, G. Gualandi, L. Baldinelli and C.O. Serlupi. 1979. Analysis of mitotic nondisjunction with Aspergillus nidulans. Environ. Health Perspect. 31: 81-95.

NCI (National Cancer Institute). 1978. Bioassay of chlorothalonil for possible carcinogenicity. DHEW Publ. NIH-78-841, NCI-CG-TR-41. NTIS PB-286369. 95 p.

Quinto, I.; G. Martire, G. Vricella, et al. 1981. Screening of 24 pesticides by Salmonella/microsome assay: Mutagenicity of benazolin, metoxuron and paraoxon. Mutat. Res. 85(4): 265.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1. U.S. EPA, Washington, DC. EPA 540/9-79-003A. NTIS PB 80-196876.

Soma, K., T. Mukai, T. Homma, M. Maho, K. Masuyama and H. Arakawa. 1980. Investigation of the residue of chlorothalonil in crops and soils. Part 2. Nippon Koshu Eisei Zasshi. 27: 643. (Jap.) (Taken from PESTAB 81:0995)

Spencer, E.Y. 1973. Guide to the Chemicals Used in Crop Protection (Research Branch, Agriculture Canada, Publ. 1093), 6th ed. University of Western Ontario, London, Ontario. p. 120. (Cited in IARC, 1983)

SRI (Stanford Research Institute) International. 1983. 1983 Directory of Chemical Producers: United States of America. SRI International, Menlo Park, CA. p. 776.

Szalkowski, M.B. and D.E. Stallard. 1977. Effect of pH on the hydrolysis of chlorothalonil. J. Agric. Food Chem. 25: 208-210.

Trotz, S.I. and J.J. Pitts. 1981. Industrial antimicrobial agents. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 13, R.E. Kirk and D.F. Othmer, Ed. John Wiley and Sons, Inc., NY. p. 248-249.

U.S. EPA. 1980. Protection of Environment. U.S. Code of Federal Regulations, Title 40, Part 180.275, p. 583. (Cited in IARC, 1983)

Wei, C.I. 1982. Lack of mutagenicity of the fungicide 2,4,5,6-tetrachloroisophthalonitrile in the Ames Salmonella/microsome test. Appl. Environ. Microbiol. 43(1): 252-254.

WHO (World Health Organization). 1975. 1974 Evaluations of Some Pesticide Residues in Food. WHO, Pestic. Residue Ser., No. 4, Geneva. p. 101-148. (Cited in IARC, 1983)

Williams, P.P. 1977. Metabolism of synthetic organic pesticides by anaerobic microorganisms. Residue Rev. 66: 63-135.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual, 7th ed. The British Crop Protection Council, Croydon, England. p. 120.

Yamaguchi, T., H. Kaneshima, M. Kumagai, et al. 1980. Considerations on prevention from poisoning by agricultural pesticides. Hokkaidoritsu Eisei Kenkyushoho. 30: 53-56. (Jap.)

Yoshikawa, H. and K. Kawai. 1966. Toxicity of phthalodinitrile and tetrachlorophthalodinitrile. I. Acute toxicity in mice. Ind. Health. 4(1-2): 11-15. (CA 66:63871a)

Zhang, Q., W. Wang, T. Han and L. Cheng. 1980. Mutagenicity of eighteen pesticides. Huan Ching K'o Hsueh. 1(5): 58-61. (Chi.) (CA 94:59426n)

APPENDIX A

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. Cincinnati, OH. 94 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. 2879-3816 p.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. 3817-5112 p.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1983. Carcinogenesis Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1983. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1982. Chemical Activities Status Report, 3rd ed. (EPACASR). Offices of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1983. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call In Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1983. CHIB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (United States International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982. USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual, 7th ed. The British Crop Protection Council, Croydon, England. p. 120.

APPENDIX B

CANCER DATA SHEET FOR DERIVATION OF q_1^*

Compound: Chlorthalonil

Reference: NCI, 1978

Species, strain, sex: Rats, Osborne-Mendel, male

Body weight: 0.47 kg (measured)

Length of exposure (le) = 560 days

Length of experiment (Le) = 777 days

Lifespan of animal (L) = 805 days

Tumor site and type: kidneys, renal tubular epithelial adenomas and carcinomas

Route, vehicle: oral, diet

Experimental Doses or Exposures	INPUT	
	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested (or Examined)
0	0	0/62
5,063 ppm • 0.05 • $\frac{560}{777}$ =	182.5	3/46
10,126 ppm • 0.05 • $\frac{560}{777}$ =	364.9	4/49

Unadjusted q_1^* from study = 5.41×10^{-4} $(mg/kg/day)^{-1}$

Human q_1^* = 2.86×10^{-3} $(mg/kg/day)^{-1}$

APPENDIX C

CANCER DATA SHEET FOR DERIVATION OF q_1^*

Compound: Chlorthalonil

Reference: NCI, 1978

Species, strain, sex: Rats, Osborne-Mendel, female

Body weight: 0.32 kg (measured)

Length of exposure (le) = 560 days

Length of experiment (Le) = 777 days

Lifespan of animal (L) = 805 days

Tumor site and type: kidneys, renal tubular epithelial adenomas and carcinomas

Route, vehicle: oral, diet

Experimental Doses or Exposures	INPUT	
	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested (or Examined)
0	0	0/62
5,063 ppm • 0.05 • $\frac{560}{777}$ =	182.5	1/48
10,126 ppm • 0.05 • $\frac{560}{777}$ =	364.9	5/50

Unadjusted q_1^* from study = 4.29×10^{-3} $(mg/kg/day)^{-1}$

Human q_1^* = 2.59×10^{-3} $(mg/kg/day)^{-1}$